Recommendations of the Michigan Advisory Committee for the Elimination of Tuberculosis (MI-ACET)

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of Michigan

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EXECUTIVE SUMMARY

Although TB cases continue to decline in Michigan and across the nation, there are still many challenges to face. The Institute of Medicine (IOM) released a report in May 2000 on the status of TB elimination in the United States entitled ***Ending Neglect: The Elimination of Tuberculosis in the United States***. In the Report, the Institute writes:

"We are now at a critical juncture. On the one hand, control of tuberculosis in the United States has been regained and we are at an all-time low in the number of new cases. On the other hand, we are particularly vulnerable again to the complacency and neglect that comes with declining numbers of cases. Now is the time to commit to the abolition of the recurrent cycles of neglect followed by resurgence that has been the history of tuberculosis. ... But to meet this goal, aggressive and decisive action beyond what is now in effect will be required."

The Michigan Advisory Committee for the Elimination of Tuberculosis (MI-ACET), a group of representatives from private and public agencies, has revised its 1995 *Recommendations of the Michigan Advisory Committee for the Elimination of Tuberculosis*. The MI-ACET was formed in 1992 with the goal of developing strategies and recommendations for the elimination of tuberculosis (TB) in Michigan. This document represents the group's efforts to provide the latest TB prevention and control strategies and contains a revised set of recommendations and strategies for a statewide coordinated approach to TB prevention, control, and elimination. It is targeted at a broad audience of private and public health care professionals, and has been prepared by representatives from those very groups. Links to more detailed information, available on the World Wide Web, have been provided throughout the body of this document as well as in the reference pages. Electronic copies of this document can be obtained by calling the Michigan Department of Community Health (MDCH) TB Program at (517) 335-8165.

MICHIGAN'S KEY RECOMMENDATIONS

- A positive TB skin test result in Michigan shall be based on the Centers for Disease Control and Prevention (CDC) guidelines.

- International students, temporary professional workers, vocational workers, and other persons arriving from countries with a high burden of TB disease, shall be tested for Latent TB Infection (LTBI).

- Health care professionals who administer and read tuberculin skin tests (TST), shall achieve certification through the TB skin test training course as identified by MDCH.

- MDCH will collaborate with the Michigan Department of Consumer and Industry Services (MDCIS) and other agencies in establishing rules for skin testing in special populations.

- Physicians, laboratories, and other health care professionals will report all cases of active and suspected TB as required by Michigan's Public Health Code.

- Directly Observed Therapy (DOT) is the standard of care for the management of all active cases of TB and selected high-risk individuals with LTBI.

- Testing for Human Immunodeficiency Virus (HIV) shall be performed on all active cases of TB.

- Accredited laboratories in the State of Michigan will comply with MDCH laboratory recommendations for TB specimen submission and testing.

- Local public health departments will utilize their authority in investigations and mandates for treatment or evaluation for TB as listed in the Public Health Code (Act 368, P.A. 1978, as amended, Section 333.5201-5207 of the Michigan Compiled Laws).

- Local public health departments shall follow MDCH recommendations regarding the U.S. Public Health Service notification system for identifying and evaluating immigrants and refugees who may be at risk for LTBI or TB disease.

- Employers whose workers are at greater risk for exposure to TB than the general population (health care facilities, correctional institutions, long-term care facilities, homeless shelters, and drug-treatment centers) shall comply with the Michigan Occupational Safety and Health Administration (MIOSHA) directives.

EPIDEMIOLOGY IN MICHIGAN

The rate of TB in Michigan has been on a steady decline, although the rate of decline is slowing. Michigan's TB case rate was 5.2 per 100,000 in 1993, and has now dropped to 3.2 in 2002. The trends are showing a substantial decline in the cases among U.S. born persons and an increase in the number of cases among foreign-born persons. The Healthy People 2010 statement of national health objectives challenges individuals, communities, and professionals to take specific steps to ensure that good health, as well as long life, are enjoyed by all. Healthy People 2010 TB objectives can be found in appendix A. Michigan specific data is available in appendix B. Additional information can be obtained from the MDCH TB Program at (517) 335-8165.

Information regarding the definition of a TB Case, for reporting purposes, can be found in appendix C.

ESSENTIAL ELEMENTS OF TB CONTROL

Targeted TB Skin Testing for LTBI

Targeted testing for TB is done to identify persons at high risk for TB disease who would benefit from treatment for latent TB infection (LTBI). Clinicians should give a TST to high-risk persons as part of their routine evaluation. QuantiFERON TB, a new blood test for identification of LTBI has recently been approved by the Food and Drug Administration (FDA). Recommendations for its use in select high-risk populations have been established by the CDC. Institutional testing is recommended for the staff of health care facilities, correctional facilities, as well as for the staff and residents of long-term care institutions where TB is found. TB testing programs for high-risk groups should be based on local epidemiology in consultation with MDCH. In Michigan, the proportion of foreign-born TB cases is

increasing. A key MI-ACET recommendation is that foreign-born persons who come to the United States with a non-resident visa status, (international students, temporary professional workers, and vocational workers) shall receive testing for LTBI upon arrival at their Michigan location as a condition for participation in the program for which they are sponsored.

Guidelines for using the QuantiFERON-TB Test for Diagnosing LTBI
http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5202a2.htm

Targeted Tuberculin Testing and Treatment of Latent Tuberculosis Infection - MMWR 2000; 49 (No. RR-6)
http://www.cdc.gov/mmwr/preview/mmwrhtml/rr4906a1.htm

Screening for Tuberculosis and Tuberculosis Infection in High-Risk Populations (ACET) - MMWR 1995; 44 (No. RR-11)
http://www.cdc.gov/mmwr/preview/mmwrhtml/00038873.htm

MI-ACET recommends TST certification. The Mantoux TST will be applied and read by designated staff that have received training and achieved certification by completion of the TST Workshop. This training includes, but is not limited to: how to apply a TST using 5 tuberculin units of purified protein derivative (PPD), how to read a TST, how to interpret a TST result, and supervised training in application and measuring of the skin test results. For more information on TST certification, contact the MDCH TB Program at (517) 335-8165.

Michigan health care providers will follow the CDC guidelines for definition of a positive skin test result, and no longer use the measurement of ≥10 mm as a positive without risk factors. The following will be considered positive in Michigan as of this publication:

≥ 5mm is classified as positive in:
- HIV-positive persons
- Recent contacts of a TB case
- Persons with fibrotic changes on chest x-ray consistent with old healed TB
- Patients with organ transplants and other immunosuppressed patients

≥10 mm is classified as positive in:
- Recent arrivals from high-prevalence countries
- Injection drug users
- Residents and employees of high risk congregate settings
- Mycobacteriology laboratory personnel
- Persons with clinical conditions that place them at high risk
- Children < 4 years of age, or children and adolescents exposed to adults in high-risk categories.

≥15 mm is classified as positive in persons with no known risk factors for TB

TST information can be found at:
http://www.cdc.gov/nchstp/tb/pubs/corecurr/Chapter_4.htm

The MDCIS requires that certain groups be screened as a condition of employment. These requirements are listed in appendix D.

MIOSHA also has requirements (MIOSHA DIRECTIVE 96-9) for testing as part of a TB control program in health care settings, drug treatment centers, homeless shelters, and correctional facilities.
http://www.michigan.gov/cis/0,1607,7-154-11407_15355-42328--,00.html

Diagnosis of Active TB

Evaluation for TB includes a medical history, physical examination, Mantoux TST, chest x-ray, and bacteriologic or histologic exam. Expert medical consultation for difficult TB case diagnosis and case management is available through the MDCH TB Program at (517) 335-8165.

Core Curriculum on Tuberculosis
http://www.cdc.gov/nchstp/tb/pubs/corecurr/Chapter_5.htm

Recommendations for Microbiological Testing

The MDCH TB laboratory provides complete mycobacterial testing services, including rapid detection of *Mycobacterium tuberculosis* in clinical specimens, identification of culture isolates of *Mycobacterium* species, determination of in vitro susceptibility to antibiotics and molecular strain typing of isolates.

Standards of testing employed and promoted by MDCH are based upon the CDC recommended methods and turnaround times (Tenover, et al.1993. J.Clin.Microbiol.31:7657-770 and Styrt, et al. 1997. J.Clin.Microbiol.35:1401). Recommendations are:

- Clinical specimens should be delivered to the laboratory for testing within 24 hours of collection.
- Reporting of results of fluorescent acid-fast slide examination within 24 hours of receipt of specimen in the laboratory.
- Use of a broth culture system for primary detection of acid-fast growth.
- Use of rapid identification methods, such as genetic probes or high-pressure liquid chromatography (HPLC) to identify isolates as *M. tuberculosis* within 21 days of receipt of specimen in the laboratory.
- Use of a rapid broth system for antibiotic susceptibility testing (AST) of primary drugs and report AST results within 28 days of receipt of specimen in the laboratory.

Michigan's Communicable Disease Rules promulgated under the authority of the Public Health Code (Act 368, P.A. 1978, as amended, Section 333.5111 of the Michigan Compiled Laws) require Michigan's clinical laboratories to submit to MDCH:

- The first *M. tuberculosis* isolate, or subculture thereof, from the individual with tuberculosis.
- Any *M. tuberculosis* isolate or subculture thereof, from a follow-up specimen, collected 90 days or more after the collection of the first *M. tuberculosis* positive specimen.

All laboratories performing testing for *M. tuberculosis* are to test according to the Clinical Laboratory Improvement Act (http://www.phppo.cdc.gov/clia) and the OSHA (http://www.cdc.gov/niosh) regulations and recommendations. Laboratory testing for *M. tuberculosis* is to be performed using a minimum of bio-safety 2 facilities and employing bio-safety level 3 practices (U.S. DHHS, CDC, NIH. 1999. Biosafety in Microbiological and Biomedical Laboratories, 4th Edition)

All agencies and health care providers submitting clinical specimens or cultures for testing must provide the name of the patient, the patient's resident address, and the name and contact information of the patient's physician or primary health care provider.

Treatment of LTBI

Treatment of LTBI is essential to controlling and eliminating TB in the United States. There are several treatment regimens available. Baseline laboratory testing is not routinely indicated for all patients at the start of treatment for LTBI. Baseline hepatic measurement of serum AST or ALT and bilirubin are indicated for patients whose initial evaluation suggests an increased risk for liver disease.
http://www.cdc.gov/nchstp/tb/pubs/corecurr/Chapter_6.htm

Update: Fatal and Severe Liver Injuries Associated with Rifampin and Pyrazinamide Treatment for Latent Tuberculosis Infection
http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5144a4.htm

Management of Persons Exposed to Multidrug-Resistant Tuberculosis - MMWR 1992; 41 (RR-11)
http://www.cdc.gov/mmwr/preview/mmwrhtml/00031296.htm

New research findings for treatment of LTBI for foreign-born persons immigrating from certain countries are available in the New England Journal of Medicine, December 5, 2002 issue (Khan et al. 2002. New Eng. J. Med. 347:1850-1859).

Treatment of TB Disease

Treatment of drug-susceptible TB disease for most patients consists of an initial 2-month phase of four drugs: isoniazid, rifampin, pyrazinamide, and ethambutol followed by a 4-month continuation phase of isoniazid and rifampin. Drug susceptibilities must drive treatment regimens. A team approach involving local health departments and other service providers is necessary for the treatment and management of each case of TB in Michigan. More information on treatment and case management of persons with TB can be found at:
http://www.cdc.gov/nchstp/tb/pubs/corecurr/Chapter_7.htm
http://www.thoracic.org/adobe/statements/treattb.pdf
http://www.umdnj.edu/ntbcweb/pr_frame.html

Treatment of multi-drug resistant TB should be undertaken **only with expert consultation.** For more information, contact the MDCH TB Program at (517) 335-8165.
http://www.cdc.gov/mmwr/preview/mmwrhtml/00031159.htm

Updated Guidelines for the Use of Rifabutin or Rifampin for the Treatment and Prevention of Tuberculosis Among HIV-Infected Patients Taking Protease Inhibitors or Nonnucleoside Reverse Transcriptase Inhibitors.
http://www.cdc.gov/mmwr/preview/mmwrhtml/mm4909a4.htm

Infection Control in Health Care Settings

The main goal of an infection control program is to identify TB disease early, isolate individuals who are suspect, and promptly treat persons who have TB. Infection control programs should include three types of controls: administrative controls, engineering controls, and personal respiratory protection, and should be based on a risk assessment of the setting.

Guidelines for Preventing the Transmission of Mycobacterium tuberculosis in Health-Care Facilities, 1994. - MMWR 1994; 43 (No. RR-13)
http://www.cdc.gov/mmwr/preview/mmwrhtml/00035909.htm

In Michigan, MIOSHA directive 96-9 specifies requirements for TB control in healthcare facilities, correctional institutions, long-term care facilities, homeless shelters, and drug treatment centers.
http://www.michigan.gov/cis/0,1607,7-154-11407_15355-42328--,00.html

BCG Vaccination

Prior receipt of Bacillus of Calmette and Guerin (BCG) vaccine is not a contraindication to the TST. The TST result should be used to support or exclude the diagnosis of LTBI. Generally, a history of BCG vaccination will not change the definition of a positive TST.

The Role of BCG Vaccine in the Prevention and Control of Tuberculosis in the United States. (ACET and ACIP) - MMWR 1996; 45 (No. RR-4)
http://www.cdc.gov/mmwr/preview/mmwrhtml/00041047.htm

Community TB Control

State and local health departments have the primary responsibility for preventing and controlling TB. Prevention and control efforts include these prioritized strategies:

1. Identifying and treating all persons who have TB disease.

2. Finding and evaluating persons who have been in contact with TB patients to determine whether they have LTBI or TB disease, and treating them appropriately.

3. Providing DOT – a strategy utilized to promote adherence to TB drug regimens. More information on DOT can be found at:
   http://www.ama-assn.org/special/hiv/library/readroom/jama98/jst71009.htm

4. Testing high-risk groups for LTBI to identify candidates for treatment of LTBI and to ensure the completion of treatment.

5. Follow the MDCH recommendations regarding the U.S. Public Health Service notification system for identifying and evaluating immigrants and refugees who may be at risk for LTBI or TB disease. Recommendations are provided in appendix E.

Surveillance and Reporting Requirements

Michigan Communicable Disease Rules stipulate the legal requirements for reporting cases or suspected cases of TB. Information on the public health code can be found at: http://www.state.mi.us/orr/emi/admincode.asp?AdminCode=Single&Admin_Num=32500171&Dpt+CH&rngHigh=.

Noncompliance Authority

The State of Michigan Communicable Disease Rules provides the authority for investigation and control of hazardous communicable diseases. The Rules and a request for medical information sample letter can be found in appendices F and K, respectively.

Appendix A

14-11. Reduce tuberculosis.

Target: 1.0 new case per 100,000 population.

Baseline: 6.8 new cases of tuberculosis per 100,000 population were reported in 1998.

Target setting method: Better than the best.

Data source: National TB Surveillance System, CDC, NCHSTP.

Total Population, 1998	**New Tuberculosis Cases**
	Rate per 100,000
TOTAL	6.8
Race and ethnicity	
American Indian or Alaska Native	11.2
Asian or Pacific Islander	34.9
Asian	DNC
Native Hawaiian and other Pacific Islander	DNC
Black or African American	17.4
White	3.8
Hispanic or Latino	13.6

Total Population, 1998	New Tuberculosis Cases
	Rate per 100,000
Not Hispanic or Latino	5.9
Black or African American	17.8
White	2.3
Gender	
Female	5.0
Male	8.6
Family income level	
Poor	DNC
Near poor	DNC
Middle/high income	DNC

DNA = Data have not been analyzed. DNC = Data are not collected. DSU = Data are statistically unreliable.

The 1989 *Strategic Plan for the Elimination of TB in the United States*[45] set a tuberculosis elimination goal of reducing TB to 1 new case per million by 2010, with an interim goal of 3.5 cases per 100,000 population by 2000. However, in the mid-1980s the trend toward TB elimination was reversed, and drug-resistant strains emerged that were even more deadly. TB cases increased by 20 percent between 1985 and 1992. Renewed efforts to combat the resurgence included improving laboratories, strengthening surveillance and expanding directly observed therapy, and expediting investigation of close contacts of TB patients. From 1993 through 1998, new cases of TB again declined, although the resurgence and related outbreaks set back TB elimination efforts by about a decade. Elimination of TB depends on significant effort and cooperation between public and private health care providers and agencies at the Federal, State, and local levels.

14-12. Increase the proportion of all tuberculosis patients who complete curative therapy within 12 months.

Target: 90 percent of patients.

Baseline: 74 percent of those tuberculosis patients reported in 1996 and started on therapy completed therapy within 12 months.

Target setting method: Better than the best.

Data source: National TB Surveillance System, CDC, NCHSTP.

Tuberculosis Patients, 1996	**Completed Curative Therapy Within 12 Months**
	Percent
TOTAL	74
Race and ethnicity	
American Indian or Alaska Native	82
Asian or Pacific Islander	75
Asian	DNC
Native Hawaiian and other Pacific Islander	DNC
Black or African American	72
White	74
Hispanic or Latino	73
Not Hispanic or Latino	74
Black or African American	72
White	75

Tuberculosis Patients, 1996	Completed Curative Therapy Within 12 Months
	Percent
Gender	
Female	75
Male	73
Family income level	
Poor	DNC
Near poor	DNC
Middle/high income	DNC

DNA = Data have not been analyzed. DNC = Data are not collected. DSU = Data are statistically unreliable.

The highest priority for TB control is to ensure that persons with the disease complete curative therapy. If treatment is not continued for a sufficient length of time, such persons often become ill and contagious again. Completion of therapy is essential to prevent transmission of the disease as well as to prevent outbreaks and the development and spread of drug-resistant TB.

Current therapy guidelines recommend that patients with drug-susceptible TB should complete a successful regimen within 12 months. Multidrug-resistant TB presents difficult treatment problems, often requiring consultation with a TB specialist and longer treatment regimens. The measurement of completion of therapy is a long-accepted indicator of the effectiveness of community TB control efforts. Health departments traditionally have reported completion-of-therapy results to CDC and have used this information locally and statewide as an evaluation measure.

14-13. Increase the proportion of contacts and other high-risk persons with latent tuberculosis infection who complete a course of treatment.

Target: 85 percent.

Baseline: 62 percent of tuberculosis contacts and other high-risk persons who started on treatment for latent TB infection in 1997 completed treatment.

Target setting method: 27 percent improvement. (Better than the best will be used when data are available.)

Data source: Aggregate Reports for TB Reports Evaluation, CDC, NCHSTP.

Data for population groups currently are not analyzed.

Treatment for latent TB infection substantially reduces the risk that TB infection will progress to disease. Certain groups are at very high risk of developing TB disease once infected. Identifiable population groups at high risk for TB vary in time and geographic area, depending on unique and changing TB-related demographics.

14-14. Reduce the average time for a laboratory to confirm and report tuberculosis cases.

Target: 2 days for 75 percent of cases.

Baseline: 21 days were needed for a laboratory to confirm and report 75 percent of TB cases in 1996.

Target setting method: 90 percent improvement.

Data source: Survey of State Public Health Laboratories, CDC, NCHSTP.

Commercially available nucleic acid amplification tests are capable of detecting *Mycobacterium tuberculosis* in a specimen within 48 hours of receipt. Concerns regarding sensitivity, cost, quality control, and special expertise requirements prevent widespread use of such tests. Upgrading TB laboratory capabilities and facilities, improving training in state-of-the-art mycobacteriology, and evaluating proficiency should better enable State public health laboratories to apply these new rapid tests to the diagnosis of TB.

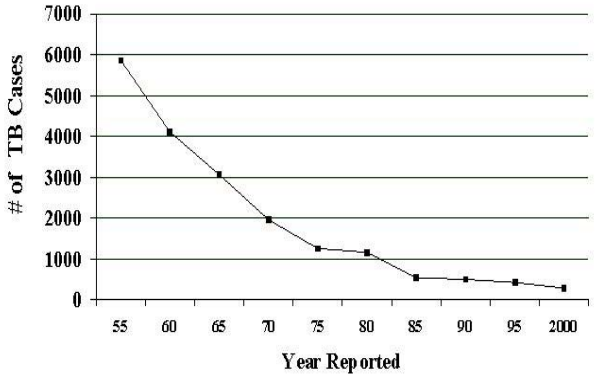
Appendix B

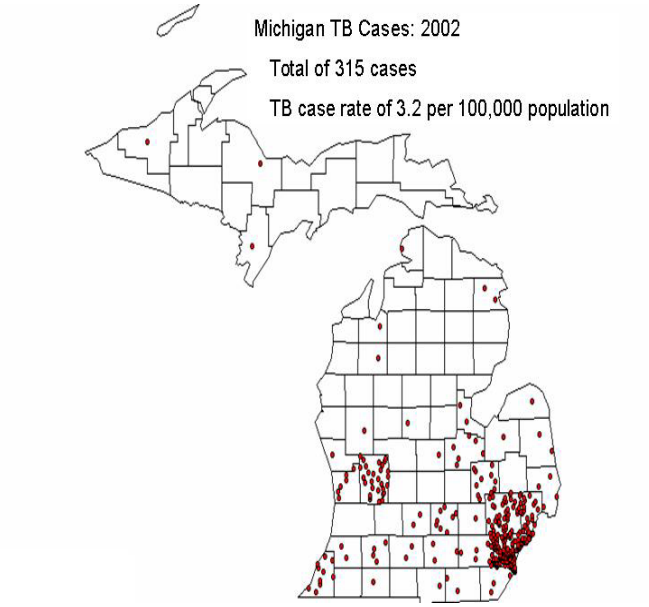
Michigan TB Epidemiology

Michigan TB Cases: 1997 - 2002

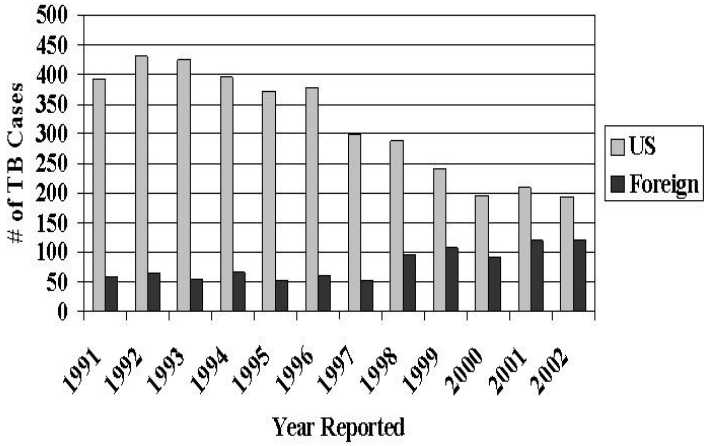
1997	1998	1999	2000	2001	2002
4.6/100,000 population	3.9/100,000 population	3.6/100,000 population	2.9/100,000 population	3.3/100,000 population	3.2/100,000 population
373	385	351	287	330	315

Michigan TB Cases: 1955 - 2000





Michigan TB Cases by National Origin: 1991 – 2002



Appendix C

Case Definitions

Excerpts from CDC's Recommendations for Counting Reported Tuberculosis Cases

Case Definition for Public Health Surveillance – For purposes of surveillance, a case of TB is defined on the basis of laboratory and/or clinical evidence of active disease due to *M. tuberculosis* complex. *M. tuberculosis* complex consists of three mycobacterial species: *M. tuberculosis, M. bovis*, and *M. africanum*. These species are identical in DNA homology studies. In terms of their ability to cause clinical disease and be transmissible from person to person, *M. bovis* and *M. africanum* behave like *M. tuberculosis*; therefore, disease caused by any of the three organisms should be reported as TB.

A. Laboratory Case Definition

Isolation of *M. tuberculosis* complex from a clinical specimen. The use of rapid-identification techniques for *M. tuberculosis* performed on a culture from a clinical specimen, such as DNA probes and high-pressure liquid chromatography (HPLC), is acceptable under this criterion.

OR

Demonstration of *M. tuberculosis* from a clinical specimen by nucleic acid amplification (NAA) test. NAA tests must be accompanied by cultures of mycobacterial species. However, for surveillance purposes, CDC will accept results obtained from NAA tests that are approved by the Food and Drug Administration (FDA). Current FDA-approved NAA tests are only approved for use on smear-positive respiratory specimens.

OR

Demonstration of acid-fast bacilli (AFB) in a clinical specimen when a culture has not been or cannot be obtained: historically this criterion has been most commonly used to diagnose TB in the postmortem setting.

B. Clinical Case Definition

In the absence of laboratory confirmation of *M. tuberculosis* complex after a diagnostic process has been completed, persons must have ALL of the following criteria for clinical TB:

Evidence of TB infection based on a positive skin test

AND

One of the following:

1. signs and symptoms compatible with current TB disease, such as an abnormal, unstable (worsening or improving) chest radiograph, or
2. clinical evidence of current disease (e.g., fever night sweats, cough, weight loss, hemoptysis)

   AND

   Current treatment with two or more anti-TB medications.

C. More detailed information regarding case definitions are available at http://www.cdc.gov/nchstp/tb/surv/surv2001/default.htm

D. More detailed information regarding the counting of cases is available at http://www.cdc.gov/nchstp/tb/surv/surv2001/pdf/AppendixC.PDF

Appendix D

MDCIS Excerpts

DEPARTMENT OF CONSUMER AND INDUSTRY SERVICES

DIVISION OF CHILD CARE CENTERS LICENSING

FAMILY AND GROUP DAY-CARE HOMES

(By authority conferred on the department of social services by section 2 of Act No. 116 of the Public Acts of 1973, as amended, being S722.112 of the Michigan Compiled Laws)

Excerpt Addressing Tuberculosis

R 400.1811 Communicable disease; exclusion of care-giving staff and day-care home family from contact with children required.

Rule 11. A person who lives in a home or cares for children who has a suspected or a confirmed case of a communicable disease shall not come into contact with children in care.

History: 1989 MR 9, Eff. Oct. 3, 1989.

R 400.1812 Health records of care-giving staff and day-care home family; record maintenance.

Rule 12. (1) A caregiver shall maintain a record that contains both of the following items:

(a) For each care-giving staff member, a statement which is signed by a licensed physician or his or her designee and which attests to the health of the staff member. The statement shall be signed within the 12-month period before care giving and every 3 years thereafter.

(b) For all care-giving staff, and for other persons who are 14 years of age or older and who live in the home, written evidence of freedom from communicable tuberculosis that is verified within 1 year before caregiving and every 3 years thereafter.

(2) If immunizations, as recommended by the department of public health, have not been given or completed for all minor children who live in the home, a caregiver shall so inform the parent of each child in care.

(3) A caregiver shall, for a period of 3 years, retain the records required by subrule (1) of this rule and the name, address, and telephone number of all persons who provided child care in the home.

DEPARTMENT OF CONSUMER AND INDUSTRY SERVICES

DIRECTOR'S OFFICE

CHILD DAY CARE LICENSING - CHILD CARE CENTERS

(By authority conferred on the director of the department of consumer and industry services by section 2 of 1973 PA 116, section 9 of 1965 PA 380, and Executive Reorganization Order No. 1996-2, MCL 722.112, 16.109, and 445.2001)

Excerpt Addressing Tuberculosis

R 400.5104b Health of staff and volunteers; report.

Rule 104b (1) A center shall have on file a report, signed by a licensed physician, for each staff member and each volunteer who has contact with children at least 4 hours per week for more than 2 consecutive weeks. This report shall declare, to the best of the physician's knowledge, the physical capability of the staff member to perform the duties required. The report shall be signed not more than 6 months before, or 30 days after, the start of employment and every 2 years thereafter.

(2) A center shall have on file evidence that each staff member and each volunteer who has contact with children at least 4 hours per week for more than 2 consecutive weeks is free from communicable tuberculosis, verified within 2 years before employment and every 2 years thereafter.

DEPARTMENT OF CONSUMER AND INDUSTRY SERVICES

DIVISION OF ADULT FOSTER CARE LICENSING

ADULT FOSTER CARE SMALL GROUP HOMES

(By authority conferred on the department of social services by section 9 of Act No. 380 of the Public Acts of 1965, as amended, and sections 10 and 13 of Act No. 218 of the Public Acts of 1979, as amended, being SS16.109, 400.710, and 400.713 of the Michigan Compiled Laws)

Excerpt Addressing Tuberculosis

R 400.14205 Health of a licensee, direct care staff, administrator, other employees, those volunteers under the direction of the licensee, and members of the household.

Rule 205. (1) A licensee, direct care staff, administrator, other employees, those volunteers under the direction of the licensee, and members of the household shall be in such physical and mental health so as not to negatively affect either the health of the resident or the quality of his or her care.

(2) A licensee shall have, on file with the department, a statement that is signed by a licensed physician or his or her designee attesting to the physician's knowledge of the physical health of the licensee and administrator. The statement shall be signed within 6 months before the issuance of a temporary license and at any other time requested by the department.

(3) A licensee shall maintain, in the home, and make available for department review, a statement that is signed by a licensed physician or his or her designee attesting to the physician's knowledge of the physical health of direct care staff, other employees, and members of the household. The statement shall be obtained within 30 days of an individual's employment, assumption of duties, or occupancy in the home.

(4) A licensee shall provide the department with written evidence that he or she and the administrator have been tested for communicable tuberculosis and that if the disease is present, appropriate precautions shall be taken. The results of subsequent testing shall be verified every 3 years thereafter.

(5) A licensee shall obtain written evidence, which shall be available for department review, that each direct care staff, other employees, and members of the household have been tested for communicable tuberculosis and that if the disease is present, appropriate precautions shall be taken as required by state law. Current testing shall be obtained before an individual's employment, assumption of duties, or occupancy in the home. The results of subsequent testing shall be verified every 3 years thereafter or more frequently if necessary.

(6) A licensee shall annually review the health status of the administrator, direct care staff, other employees, and members of the household. Verification of annual reviews shall be maintained by the home and shall be available for department review.

(7) A licensee shall obtain certification from a volunteer that the volunteer is free from communicable disease and that the volunteers physical and mental health will not negatively affect either the health of the resident or the quality of the resident's care.

DEPARTMENT OF CONSUMER AND INDUSTRY SERVICES

DIVISION OF ADULT FOSTER CARE LICENSING

ADULT FOSTER CARE LARGE GROUP HOMES

(By authority conferred on the department of social services by section 9 of Act No. 380 of the Public Acts of 1965, as amended, and sections 10 and 13 of Act No. 218 of the Public Acts of 1979, as amended, being SS16.109, 400.710, and 400.713 of the Michigan Compiled Laws)

Excerpt Addressing Tuberculosis

R 400.15205 Health of a licensee, direct care staff, administrator, other employees, those volunteers under the direction of the licensee, and members of the household.

Rule 205. (1) A licensee, direct care staff, administrator, other employees, those volunteers under the direction of the licensee, and members of the household shall be in such physical and mental health so as not to negatively affect either the health of the resident or the quality of the resident's care.

(2) A licensee shall have, on file with the department, a statement that is signed by a licensed physician or his or her designee attesting to the physician's knowledge of the physical health of the licensee and administrator. The statement shall be signed within 6 months before the issuance of a temporary license and at any other time requested by the department.

(3) A licensee shall maintain, in the home, and make available for department review, a statement that is signed by a licensed physician or his or her designee attesting to the physician's knowledge of the physical health of direct care staff, other employees, and members of the household. The statement shall be obtained within 30 days of an individual's employment, assumption of duties, or occupancy in the home.

(4) A licensee shall provide the department with written evidence that he or she and the administrator have been tested for communicable tuberculosis and that if the disease is present, appropriate precautions shall be taken. The results of subsequent testing shall be verified every 3 years thereafter.

(5) A licensee shall obtain written evidence, which shall be available for department review, that each direct care staff, other employees and members of the household have been tested for communicable tuberculosis and that if the disease is present, appropriate precautions shall be taken as required by state law. Current testing shall be obtained before an individual's employment, assumption of duties, or occupancy in the home. The results of subsequent testing shall be verified every 3 years thereafter or more frequently if necessary.

(6) A licensee shall annually review the health status of the administrator, direct care staff, other employees and members of the household. Verification of annual reviews shall be maintained by the home and shall be available for department review.

(7) A licensee shall obtain certification from a volunteer that the volunteer is free from communicable disease and that the volunteer's physical and mental health will not negatively affect either the health of the resident or the quality of the residents care.

Appendix E

Recommendations on the Follow-Up and Assessment of Persons with Class B1/B2 Tuberculosis

The proportion of foreign-born cases of tuberculosis (TB) in the State of Michigan has increased from 12.3% in 1995 to 38% in 2002. Nationally, cases among foreign-born individuals increased from 22% of the national total in 1986 to 49% in 2001. Estimates suggest that by the end of 2002, half of U.S. cases may occur in foreign-born individuals. These changes reflect the global magnitude of TB as a significant public health problem and the importance of the B notification program as a screening strategy to identify immigrants and refugees who have a high risk for TB.

The overseas screening process is intended to exclude infectious persons from entering the United States and to ensure that new arrivals who have active TB or who are at high risk for TB receive medical services. Visa applicants 15 years of age or older must have a chest radiograph (CXR) performed overseas. If the CXR is suggestive of active pulmonary TB, sputa for acid-fast bacillus (AFB) smears must be obtained. Applicants are then classified as described in the table below:

Immigrant/Refuge Classification	Overseas CXR	Overseas Sputum AFB Smears	Restrictions
A Waiver*	Abnormal, suggestive of active TB	Positive	May not enter the U.S. until started on anti-TB therapy and sputum smears are negative, and: 1) Apply for a waiver signed by the local health department in their intended U.S. destination (A waiver) or 2) Complete TB therapy overseas
B1	Abnormal, suggestive of active TB	Negative	Instructed to report to the local health department in the U.S. for further medical evaluation within 30 days of arrival
B2	Abnormal, suggestive of inactive TB	Not done	Same as above

*** Very few persons with A waivers will be entering the country, so they will not be included in this information**.

When a person with Class B1/B2 TB moves to the U.S., the Centers for Disease Control and Prevention (CDC), Division of Quarantine notifies the local health jurisdiction in the individual's intended county of residence that medical follow-up is necessary. A copy of this notice is also sent to the State TB Program. The person is instructed to report to the local health department within one month of arrival. Because individuals classified as B1/B2 are at an increased risk for having or developing active TB, follow-up should be given the same priority as a contact investigation.

The primary purpose of the follow-up evaluation is to identify and treat all active cases of TB. However, a secondary purpose is to identify persons with a positive TB skin test (TST) who are eligible for treatment of latent TB infection (LTBI).

An in-person evaluation of the B1/B2 classified individual should include:

1. Review of overseas CXR to determine if there is evidence of TB disease. Repeat the CXR if the following applies:

    a. Overseas CXR is not available, is technically inadequate, or
    b. Suspicion for TB is high enough that the patient is being started on treatment for suspected active TB disease, or
    c. Abnormalities seen on the overseas CXR are highly suspicious for active TB disease and it was taken more than three months ago.

2. Interview the patient to obtain information on medical history. This should include a history of known exposure to TB, prior TB diagnosis or treatment, prior TST results, and any indications or contraindications to a course of treatment for LTBI.

3. Provide TST for all B1/B2 individuals with no history of a prior positive reaction.

4. Collect sputum specimens for AFB smear and culture from persons who are suspected of having active TB disease.

5. Return to the Michigan Department of Community Health TB Program, the CDC 75.17 evaluation form (copy enclosed).

Recommendations from the CDC and the Michigan Advisory Committee for the Elimination of Tuberculosis (MI-ACET) have emphasized the screening of high-risk populations for TB, including recent immigrants from areas of the world with a high prevalence of TB. Meeting the needs of this population today is the most cost-effective and efficient way to reduce our state's TB burden in the future.

Appendix F

Communicable Disease Rules

Components of the Michigan Communicable Disease Rules as it relates to confinement of Tuberculosis patients.

PART 52. HAZARDOUS COMMUNICABLE DISEASES

333.5201 Definitions and principles of construction.

Sec. 5201. (1) As used in this part:

(a) "Carrier" means an individual who serves as a potential source of infection and who harbors or who the department reasonably believes to harbor a specific infectious agent or a serious communicable disease or infection, whether or not there is present discernible disease.

(b) "Health threat to others" means that an individual who is a carrier has demonstrated an inability or unwillingness to conduct himself or herself in such a manner as to not place others at risk of exposure to a serious communicable disease or infection. Health threat to others includes, but is not limited to, 1 or more of the following:

(i) Behavior by the carrier that has been demonstrated epidemiologically to transmit, or that evidences a careless disregard for transmission of, a serious communicable disease or infection to others.

(ii) A substantial likelihood that the carrier will transmit a serious communicable disease or infection to others, as evidenced by the carrier's past behavior or statements made by the carrier, that are credible indicators of the carrier's intention to do so.

(iii) Affirmative misrepresentation by the carrier of his or her status as a carrier before engaging in behavior that has been demonstrated epidemiologically to transmit the serious communicable disease or infection.

(2) In addition, article I contains general definitions and principles of construction applicable to all articles in this code and part 51 contains definitions applicable to this part.

History: 1978, Act 368, Eff. Sept. 30, 1978;--Am. 1988, Act, 490, Eff. Mar. 30, 1989.

333.5203 Warning notice generally.

Sec. 5203. (1) Upon a determination by a department representative or a local health officer that an individual is a carrier and is a health threat to others, the department representative or local health officer shall issue a warning notice to the individual requiring the individual to cooperate with the department or local health department in efforts to prevent or control transmission of serious communicable diseases or infections. The warning notice may also require the individual to participate in education, counseling, or treatment programs, and to undergo medical tests to verify the person's status as a carrier.

(2) A warning notice issued under subsection (1) shall be in writing, except that in urgent circumstances, the *warning notice* may be an oral statement, followed by a written statement within 3 days. A warning notice shall be individual and specific and shall not be issued to a class of persons. A written *warning notice* shall be served either by registered mail, return receipt requested, or personally by an individual who is employed by, or under contract to, the department or a local health department.

(3) A warning notice issued under subsection (1) shall include a statement that unless the individual takes the action requested in the warning notice, the department representative or local health officer shall seek an order from the probate court, pursuant to. this part. The *warning notice* shall also state that, except in cases of emergency, the individual to whom the warning notice is issued has the right to notice and a hearing and other rights provided in this part before the probate court issues an order.

History: 1978, Act 368, Eff. Sept. 30, 1978;--Am. 1988, Act 490, Eff. Mar. 30, 1989.

**333.5205 Failure or refusal to comply with warning notice; petition; hearing; notice; waiver; orders;
recommendation and duties of commitment review panel; appeal to probate court; termination or
continuation of commitment; cost of implementing order; Fight to counsel; appeal to circuit court;
leaving facility as contempt.**

Sec. 5205. (1) If a department representative or a local health officer knows or has reasonable grounds to believe that an individual has failed or refused to comply with a warning notice issued under section 5203, the department or local health department may petition the probate court for the county of Ingham or for the county served by the local health department for an order as described in subsection (3).

(2) A petition filed under subsection (1) shall state all *of* the following:

(a) The grounds and underlying facts that demonstrate that the individual is a health threat to others and, unless an emergency order is sought under section 5207, has failed or refused to comply with a warning notice issued under section 5203.

(b) The petitioner's effort to alleviate the health threat to others before the issuance of the *warning notice,* unless an emergency order is sought under section 5207.

(c) The type of relief sought.

(d) A request for a court hearing on the allegations set forth in the petition.

(3) Upon receipt of a petition filed under subsection (1), the probate court shall fix a date for hearing that shall be as soon as possible, but not later than 14 days after the date the petition is filed. Notice of the petition and the time and place of the hearing shall be served personally on the individual and the petitioner not less than 3 days before the date of the hearing. Notice of the hearing shall include notice of the individual's right to appear at the hearing, the right to present and cross-examine witnesses, and the right to counsel as provided in subsection (7). The individual and the petitioner may waive notice of hearing, and upon filing of the waiver in writing, the probate court may hear the petition immediately.

(4) Upon a finding by the probate court that the department or local health department has proven the allegations set forth in the petition by clear and convincing evidence, the probate court may issue I or more of the following orders:

(a) An order that the individual participate in a designated education program.

(b) An order that the individual participate in a designated counseling program.

(c) An order that the individual participate in a designated treatment program.

(d) An order that the individual undergo medically accepted tests to verify the individual's status as a carrier or for diagnosis.

(e) An order that the individual notify or appear before designated health officials for verification of status, testing, or other purposes consistent with monitoring.

(f) An order that the individual cease and desist conduct that constitutes a health threat to others.

(g) An order that the individual live part-time or full-time' in a supervised setting for the period and under the conditions set by the probate court.

(h) Subject to subsection (5), an order that the individual be committed to an appropriate facility for the period and under the *conditions set* by the probate court. A commitment ordered under this subdivision shall not be for more than 6 months, unless the director of the facility, upon motion, shows good cause for continued commitment.

(i) Any other order considered just by the probate court.

(5) The probate court shall not issue an order authorized under subsection (4)(h) unless the probate court first considers the recommendation of a commitment review panel appointed by the probate court under this subsection to review the need for commitment of the individual to a health facility. The commitment review panel shall consist of 3 physicians appointed by the probate court from a list of physicians submitted by the department. Not less than 2 of the physicians shall have training and experience in the diagnosis and treatment of serious communicable diseases and infections. However, upon the motion of the individual who is the subject of the order, the probate court shall appoint as 1 member of the commitment review panel a physician who is selected by the individual. The commitment review panel shall do all of the following:

(a) Review the record of the proceeding.

(b) Interview the individual, or document the reasons why the individual was not interviewed.

(c) Recommend either commitment or an alternative or alternatives to commitment, and document the reasons for the recommendation.

(6) An individual committed to a facility under subsection (4) (h) may appeal to the probate court for a commitment review panel recommendation as to whether or not the patient's commitment should be terminated. Upon the filing of a claim of appeal under this subsection, the probate court shall reconvene the commitment review panel appointed under subsection (5) as soon as practicable, but not more than 14 days after the filing of the claim of appeal. Upon reconvening, the commitment review panel shall do all of the following:

(a) Review the appeal and any other information considered relevant by the commitment review panel.

(b) Interview the individual, or document the reasons why the individual was not-interviewed.

(c) Recommend to the probate court either termination or continuation of the commitment, and document the reasons for the recommendation.

(7) Upon receipt of the recommendation of the commitment review panel under subsection (6), the probate court may terminate or continue the commitment.

(8) The cost of implementing an order issued under subsection (4) shall be borne by the individual who is the subject of the order, unless the individual is unable to pay all or a part of the cost, as determined *by* the probate court. If the probate court determines that the individual is unable to pay all or a part of the cost of implementing the order, then the state shall pay all of the cost or that part of the cost that the individual is unable to pay, upon the certification of the department.

(9) An individual who is the subject of a petition filed under this section or an affidavit filed under section 5207 shall have the right to counsel at all stages of the proceedings. If the individual is unable to pay the cost of counsel, the probate court shall appoint counsel for the individual.

(10) An order issued by the probate court under this section may be appealed to the circuit court. The circuit court shall hear the appeal within 30 days after the date the claim of appeal is filed with the circuit court. However, an order issued *by* the probate court under this section shall not be stayed pending appeal, unless ordered by the circuit court on motion for good cause.

(11) An individual committed to a facility under this section who leaves the facility before the date designated in the commitment order without the permission of the probate court is guilty of contempt.

History: Add. 1988, Act 490, Eff. Mar. 30, 1989.

Compiler's note: In subsection (3), the phrase "as provided in subsection (7)" evidently should read "as provided in subsection (9),

333.5207 Protection of public health in emergency; affidavit; probate court order; taking individual
into custody; transporting individual to emergency care or treatment facility; temporary detention;
notice of hearing;. continued temporary detention; petition.

Sec. 5207. (1) To protect the public health in an emergency, upon the filing of an affidavit by a department representative or a local health officer, the probate court may order the department representative, local health officer, or a peace officer to take an individual whom the probate court has reasonable cause to believe is a carrier and is a health threat to others into custody and transport the individual to an appropriate emergency care or treatment facility for observation, examination, testing, diagnosis, or treatment and, if determined necessary by the probate court, temporary detention. If the individual is already institutionalized in a facility, the court may order the facility to temporarily detain the individual. An order issued under this subsection may be issued in an ex parte proceeding upon an affidavit of a department representative or a local health officer. The probate court shall issue an order under this subsection upon a determination that reasonable cause exists to believe that there is a substantial likelihood that the individual is a carrier and a health threat to others. An order under this subsection may be executed on any day and at any time, and shall be

served upon the individual who is the subject of the order immediately upon apprehension or detention.

(2) An affidavit filed by a department representative or a local health officer under subsection (1) shall set forth the specific facts upon which the order is sought including, but not limited to, the reasons why an emergency order is sought.

(3) An individual temporarily detained under subsection (1) shall not be detained longer than 72 hours, excluding Saturdays, Sundays, and legal holidays, without a court hearing to determine if the temporary detention should continue.

(4) Notice of a hearing under subsection (3) shall be served upon the individual not less than 24 hours before the hearing is held. The notice shall contain all of the following information:

(a) The time, date, and place of the hearing.

(b) The grounds and underlying facts upon which continued detention is sought.

(c) The individual's right to appear at the hearing.

(d) The individual's right to present and cross-examine witnesses.

(e) The individual's right to counsel, including the right to counsel designated by the probate court, as described in section 5205(9).

(5) The probate court may order that the individual continue to be temporarily detained if the court finds, by a preponderance of the evidence, that the individual would pose a health threat to others if released. An order under this subsection to continued temporary detention shall not continue longer than 5 days, unless a petition is filed under section 5205. If a petition is filed under section 5205, the temporary detention shall continue until a hearing on the petition is held under section 5205.

History: Add. 1988, Act 490, Eff. Mar. 30, 1989.

333.5211-333.5269 Repealed. 1988, Act 491, Eff. Mar. 30, 1989.

Compiler's note: The repealed sections pertained to hazardous communicable diseases.

PART 53. EXPENSE OF CARE

333.5301 County chargeable with expense of care; reimbursement by state; individuals with tuberculosis or honorable discharges considered domiciled in state at large; expense of care paid by state on certification of department; reasonableness of claims and accounts; appeal.

Sec. 5301 . (I) The county in which an individual receiving care under section 5117 has a domicile is chargeable with the expense of the care, and this state shall reimburse that county for all or a portion of the expense in the amounts the legislature appropriates for that purpose. An individual who has tuberculosis and has not acquired a legal settlement in this state in accordance with the social welfare act, Act No. 280 of the Public Acts of 1939, being sections 400.1 to 400.121 of the Michigan Compiled Laws, or an individual who was honorably discharged from a branch of the military services of the United States and not otherwise hospitalized for the purpose of this part shall be considered to be domiciled in this state at large, and the expense of that individual's care, while the care continues with the approval of the department, shall be paid by the state on certification of the department. The reasonableness and propriety of all claims and accounts under this subsection shall be passed upon and determined by the department, subject to appeal to the circuit court for the county of Ingham as to questions of law.

(2) An individual committed to an inpatient facility for tuberculosis pursuant to a probate court order under section 5205 and not otherwise hospitalized for the purpose of part 51 or 52 shall be: considered to be domiciled in this state at large, and the expense of that individual's care, while the care continues with the approval of the department, shall be paid by the state on certification of the department. The reasonableness and propriety of all claims and accounts under this subsection shall be passed upon and determined by the department, subject to appeal to the circuit court for the county of Ingham as to questions of law.

History: Add. 1988, Act 491, Eff. Mar. 30, 1989.

333.5303 Care provided where individual found at expense of county where individual domiciled; notice; return of individual to county of domicile; disputed or contested claim arising between 2 or more counties; decision.

Sec. 5303. (1) Upon determination by the county department of social services that the place of domicile of an individual receiving care under section 5117 is in another county in this state, care shall be provided where the individual is found at the expense of the county where the individual is domiciled. The county department of social services, not later than I month after the commencement of care, shall mail written notice that the care is being provided to the local department of social services of the individual's county of

domicile. The local health department of the county of domicile may provide for the return of the individual to, and care in, that county.

(2) If the domicile of the individual is not acknowledged by the alleged county of domicile within I month after mailing the notice under subsection (1), the question of domicile may be submitted for decision to the state department of social services. If a disputed or contested claim arises between 2 or more counties as to the county of domicile, the director of social services shall determine the county of domicile when so requested or on his or her own motion. The decision of the director of social services is final. However, pending determination, the county in which the individual is found shall, provide the necessary care.

History: Add. 1988, Act 491, Eff. Mar. 30, 1989.

333.5305 Determination that county where individual found not county of domicile; reimbursement.

Sec. 5305. Upon determination by the director of social services that the county where the individual is found is not the county of domicile, the county of domicile, as determined by the director of social services, shall reimburse the county where the individual is found for all expenses incurred, less any reimbursements from the state or other source for the care.

History: Add. 1988, Act 491, Eff. Mar. 30, 1989.

333.5307 Expenditure under S 333.5117 considered expenditure for protection of public health, not
welfare or relief; reimbursement; notice and hearing; finding; order; distribution of receipts.

Sec. 5307. An expenditure of public funds under section 5117 for the care of an individual is considered an expenditure for the protection of the public health, and not money advanced as welfare or relief. An individual is not legally obligated to reimburse the expense incurred, unless the department and the county of domicile, after reasonable notice and upon a hearing, find that the individual hospitalized or treated, or the persons legally liable for the individual's support, are possessed of sufficient income or estate to enable them to make the reimbursement in whole or in part without materially affecting their reasonable economic security or support, in view of their respective resources, obligations, and responsibilities to dependents and order reimbursement. The order shall not be made retroactive unless the department and the county of domicile find that the person to be charged is guilty of misrepresenting or withholding knowledge of facts material to the issue. Receipts under the order, and money voluntarily paid as reimbursement, shall be distributed pro rata to the funds out of which the expenditure was made.

Appendix G

Current Tuberculosis Research in Michigan

Virulence Related Genetic Variation of *Mycobacterium tuberculosis* Strains

Principal investigator:

Zhenhua Yang, M.D., Ph. D.,
Assistant Professor, Department of Epidemiology
University of Michigan, School of Public Health

Tuberculosis (TB) remains the leading infectious cause of global mortality. The emergence of drug resistant TB and a deadly synergy with HIV seen in recent years highlight the need for a better understanding of TB transmission and pathogenesis. The long term objectives of this project are: 1) to identify underlying genetic factors of *Mycobacterium tuberculosis* important to the pathogenesis and the epidemiology of TB and 2) to provide targets for the development of more efficient vaccine and therapeutical agents for TB prevention and control. The hypothesis for the present project is that survival of successful bacterial pathogens not only depends on their ability to alter global patterns of gene expression in response to the changing environments during infection, but also depends on the presence or absence of certain genes in the bacteria that play an important role in virulence, and that loss or gain of such genes in clinical strains of *M. tuberculosis* is associated with their infectivity and pathogenicity. The specific aims and the related experimental strategies are: 1) to determine genomic variation among *M. tuberculosis* strains associated with different epidemiological and clinical characteristics by genomic subtraction and to identify DNA sequence unique to epidemiologically and clinically successful strains of *M. tuberculosis* in comparison with epidemiologically and clinically less successful strains and also with completely sequenced strains of *M. tuberculosis*, H37Rv and CDC 1551; 2) to assess the potential importance of the subtraction sequence to TB transmission and pathogenesis by screening for the presence or absence of the fragments in epidemiologically and clinically well characterized clinical isolates collected in population-based molecular epidemiological study of TB, and to determine the relative distribution of these subtraction sequences by epidemiological and clinical co-variates; and 3) to identify and to characterize genes contained in the subtraction products which are associated with TB transmission and pathogenesis and to create mutant strains for gene functional analysis. By combining epidemiological information with molecular genetics, the investigators are conducting a focused search for genes associated with transmission and pathogenesis.

Molecular Epidemiology of Tuberculosis

Principal investigator:

Zhenhua Yang, M.D., Ph. D.,
Assistant Professor, Department of Epidemiology
University of Michigan, School of Public Health

The disease burden of TB in populations are influenced by the risk of an individual in the community being infected with tubercle bacilli in a given time period, the risk of disease following such infection, and the risk of disease occurring long after the original infection owing to the reactivation of latent infection. Epidemiological investigations have sought to measure these risks and to identify factors that modify them, particularly those factors that might be susceptible to change through specific intervention measures. By integration of the molecular techniques to track specific strains of pathogen with conventional epidemiological approaches to understanding the distribution of disease in populations, Dr. Yang's lab conducts molecular epidemiological studies, aiming at understanding the dynamics of TB transmission in different populations, defining the human and environmental factors associated with risks for acquiring infection with *M. tuberculosis*, and answering the longstanding question regarding the relative contribution of disease due to the reactivation of latent infection and disease due to progression of currently acquired infection to the burden of TB in populations, including those in developing countries where the vast majority of the disease burden falls.

The Dynamics of Granuloma Formation in Tuberculosis

Principal investigator:

Denise E. Kirschner, Ph. D.,
Associate Professor, Department of Microbiology and Immunology
University of Michigan, Medical School

The goal of this proposal is to explain the formation of granuloma in infection with *M. tuberculosis*. Understanding granuloma formation and function will elucidate the primary immune mechanism for controlling tuberculosis infection. The goal of the study is to simulate the process of granuloma formation on a spatio-temporal scale and present the results in a time-lapse movie format. This will yield an interactive tool to study the role of specific immune elements in granuloma formation and function. Development of a virtual model of human infection will allow for integration of the plethora of chemokine, cytokine, cellular influx information and other relevant immunological factors, as generated by experimental systems. To this end, powerful techniques (e.g., microarrays) are available for obtaining comprehensive gene expression

data. Using these methods to survey expression within the granulomas of non-human primates and mice will enable us to determine which immunological mediators are involved in granuloma formation, what the timing of their expression is in the formation, and their location within the granuloma. Further studies will indicate which cell-types are expressing which mediators. Our specific aims are to: (1) Identify the temporal and spatial expression of host immune elements participating in granuloma formation using gene expression tools in murine models of tuberculosis (2) Identify the temporal and spatial expression of host immune elements participating in granuloma formation using gene expression tools in murine models of tuberculosis (3) Determine the dynamics of granuloma formation and function in humans using mathematical models of the granuloma response in tuberculosis. Through this unique approach, the interaction of multiple factors that control the formation of the granuloma will be defined. Key parameters governing these interactions will be identified. The ability to synthesize the data generated by the experiments in the models allows for an understanding of the dynamics of granuloma formation as more than the sum of its parts.

Modeling Cellular Immunity During HIV and TB Infections

Principal investigator:

Denise E. Kirschner, Ph. D.,
Associate Professor, Department of Microbiology and Immunology
University of Michigan, Medical School

The goal of this proposal is to explain the role of TH1-type and TH2-type cytokine profiles in disease progression for the pathogens human immunodeficiency virus type 1 (HIV-1) and *Mycobacterium tuberculosis*. The investigators examine the following hypotheses: (1) The progression of disease during the pathogenesis of HIV infection is dependent upon a long-term shift of TH1- and TH2-type cytokines that are expressed during the evolution of the disease. This paradigm would predict that a dominant phenotype characterized by TH2-type cytokines is present in end-stage disease. (2) The establishment and maintenance of latency in infection with *Mycobacterium tuberculosis* may be predicted based on the cytokine profiles, balancing the tissue damaging response with resolution. The overall objective of the project is to formulate mathematical models based on the complex cytokine network in the cellular immune response to disease. The three specific aims are: (1) Determine the predictive role of a TH1/TH2 cytokine balance in differentiating the disease outcomes in infection with *Mycobacterium tuberculosis*. Specifically, we will investigate why most individuals develop latent TB infection, yet others progress to disease, via either a fast or slow progression. (2) Explore the role of a long-term TH1/TH2 cytokine shift expressed during HIV-1 disease progression and to determine the predictive role of a TH1/TH2 cytokine imbalance in that progression. (3) Investigate the use of

cytokines as therapeutic agents of immunotherapy, either alone or in conjunction with chemotherapy, for both latent and progressive disease of both drug-resistant and drug-sensitive HIV-1 and *M. tuberculosis*. These results are also expected to lead to a greater understanding of co-infections with HIV-1 and TB. Mathematical models will be developed that reflect the dynamics of the different diseases as well as disease states. These models include experimental data and will be analyzed using mathematical approaches for characterizing nonlinear dynamical systems. The interaction of multiple factors that control, activate or facilitate the cellular-immune response to the pathogens will be defined. Key parameters governing these interactions will be identified through mathematical sensitivity analyses. These results will incorporate, and be tested against, known clinical and experimental data.

Protection from Aminoglycoside Ototoxicity

Principal investigator:

Jochen H. Schacht,
Professor & Director, KHRI
Department of Otolaryngology
University of Michigan, Medical School

The development of a therapeutic strategy to prevent aminoglycoside-induced hearing loss seems more urgent than ever. Millions of patients are treated annually in the US; worldwide, aminoglycosides are the most commonly used antibiotics. The problem is aggravated by the global resurgence of tuberculosis and the increased occurrence of resistant bacteria that necessitate multi-drug regimens including aminoglycosides. Given the 10 to 20 percent incidence of cochlear and vestibular disturbances associated with aminoglycoside treatment, this constitutes a major health problem in the US and abroad. The goal of the proposed research is to develop a rational protective treatment against aminoglycoside-ototoxicity. The anticipated studies are founded on exciting recent discoveries from this laboratory that allow the proposal of a mechanism of toxicity and a pharmacological means of protection. The first successful tests of the proposal of a mechanism of toxicity and a pharmacological means of protection. The first successful tests of the protective strategy have already been completed in guinea pig. The approach is based on the novel hypothesis that gentamycin can chelate iron. The iron-gentamycin complex catalyzes free-radical reactions that are toxic to the cell. These reactions can be inhibited by radical scavengers and, most dramatically, by iron chelators who attenuate gentamycin-induced hearing loss in guinea pigs. The goals of the proposal will be primarily accomplished by experiments on prevention or amelioration of aminoglycoside ototoxicity in guinea pigs in vivo. In vitro and in vivo experiments will establish efficacious and safe combinations of iron chelators and scavengers. These goals are aided by structural and

chemical analyses of the iron-aminoglycoside complexes, which will improve our understanding of the underlying mechanisms and guide the development of protective strategies. These questions will be addressed with well-established biochemical, physiological, analytical and physicochemical techniques. The prevention or amelioration of adverse effects of aminoglycoside antibiotics will have far reaching implications for the continued but safe use of a family of drugs whose primary efficacy is unquestioned.

Oxidant Induced BETA Chemokines in Grannuloma Formation

Principal investigator:

Jeffery S. Warren, M.D.
Professor and Director of Clinical Pathology
Department of Pathology
University of Michigan, Medical School

The spectrum of granulomatous lung disease is broad, encompassing diseases caused by readily identifiable microbial agents (e.g. tuberculosis, schistosomiasis), foreign particulates (e.g. berylliosis, talcosis), and diseases in which no causative agent has been identified (e.g. Wegener's granulomatosis, sarcoidosis). Central to granuloma formation is the coordinated recruitment of mononuclear phagocytes, and in some types of lesions, T lymphocytes, into discrete anatomic foci. Intravenous infusion of particulate yeast cell wall glucan into rats results in the synchronous development of foreign body-type granulomas that are composed almost entirely of monocytes and macrophages. Monocyte chemoattractant protein-1 (MCP-1) activity is required for full development of granulomas. There is an early (1-4 hrs.) blood vessel wall-associated rise in MCP-1 and a later (6-24 hrs.) rise in MCP-1 activity that is associated with granuloma cells per se. The early rise in MCP-1 activity is temporally and anatomically associated with the transient influx of neutrophils into vessel walls (at sites of glucan embolization). Likewise, in *Mycobacterium bovis* (BCG)-infected mice, there is an early, transient influx of neutrophils into sites of subsequent pulmonary granuloma formation. In contrast to glucan-induced granulomas, hypersensitivity-type *M. bovis* (BCG)-induced lesions contain T lymphocytes. Completed studies suggest that the recruitment of mononuclear cells into evolving lung granulomas is orchestrated in part by monocyte chemotactic beta chemokines such as MCP-1. Regulated upon activation, normal T-cell expressed and presumably secreted (RANTES) macrophage inflammatory protein 1alpha (MIP-1alpha) and MIP 1beta. The investigators hypothesize that the early expression of these peptides within localized segments of blood vessel walls is induced by products of neutrophils, specifically, reactive oxygen intermediates (ROIs). The role of neutrophils and ROIs in the induction of beta-chemokines will be studied *in vivo* and *in vitro*. Time course and topographic analyses of beta

chemokine (MCP-1, RANTES, MIP-1alpha. MIP-1beta) mRNA and protein expression during evolving glucan and *M. bovis* (BCG-induced pulmonary granulomatosis will be carried out by Northern and dot hybridization, in situ hybridization, and immunohistochemistry. Granuloma development and beta-chemokine expression will be examined in neutrophil-sufficient, neutrophil-depleted, and specific antioxidant-treated animals. Finally, biochemical and molecular mechanisms of neutrophil ROI-induced beta-chemokine expression will be systematically examined in isolated human endothelial cells, alveolar type II epithelial cells, and fibroblasts (vessel wall constituents). The proposed *in vitro* studies will focus on how ROI-dependent cellular redox status modulates the expression of beta- chemokines.

Examination of emergence of antimycobacterial drug resistance and evaluation
of different methods to prevent the development of drug resistance

Principle investigator:

Diane Marie Cappelletty, Pham. D.
Assistant Professor
Wayne State University, College of Pharmacy & Allied Health Pharmacy Practice

Dr. Cappelletty's laboratory is working with an in vitro 2-compartment infection model that is capable of simulating human pharmacokinetic parameters for antibiotics. Simulated human doses of antibiotics are administered into the central compartment of the model and the pharmacodynamic effects of the drug on the organisms in the infection compartment are assessed. This model is used to evaluate the effect of different drug regimens on resistant gram-negative bacilli. The model allows examining the development of resistance to different antimicrobial agents in order to prevent the emergence of resistance with combination therapies and different methods of drug administration. In addition, Dr. Cappelletty's laboratory is also working with an *in vitro* intracellular model for mycobacterial infections, which has the capability to simulate human pharmacokinetic characteristics of antimycobacterial drugs. This is one of the first pharmacokinetic /pharmacodynamic models for mycobacterial infections. By using this model, they examine the rates and extents of killing over the short- and long-term treatment duration of both mono-drug therapy and combination therapy. They also examine the emergence of resistance to the various agents and evaluate different methods to prevent the development of drug resistance.

Appendix H

Internet Resources

Centers for Disease Control and Prevention
Division of Tuberculosis Elimination
www.cdc.gov/nchstp/tb

American Thoracic Society
http://www.thoracic.org/

American Lung Association
http://www.lungusa.org/diseases/lungtb.html

American Lung Association of Michigan
http://www.alam.org/research/thoracic_society.asp

National Tuberculosis Controllers Association
http://www.ntca-tb.org/

National Model TB Centers

Francis J. Curry National TB Center
San Francisco, CA
www.nationaltbcenter.edu

Charles P. Felton National TB Center at Harlem Hospital
New York, NY
www.harlemtbcenter.org

New Jersey Medical School National TB Center
Newark, NJ
www.umdnj.edu/ntbcweb

International Resources

World Health Organization
www.who.int/gtb/

International Union Against Tuberculosis and Lung Disease
http://www.iuatld.org/full_picture/en/frameset/frameset.phtml

Stop TB Initiative
http://www.stoptb.org/

Appendix I

Michigan Advisory Committee for the Elimination of Tuberculosis (MI-ACET) Resource Directory

Issues/Concerns/Questions	Contact Persons
Michigan TB Recommendations Michigan TB Guidelines Michigan TB Policies National TB Information	Gabe Palumbo, MBA, MPH CDC Public Health Advisor - MDCH (517) 335-8798 Sue Spieldenner, RN TB Program Coordinator - MDCH (517) 335-8165
TB Education	Teri Lee Dyke, RN, BSN, CIC Regional TB Nurse - American Lung Association of Michigan – Southeastern Michigan (517) 484-7283 Julie McCallum, RN, MPH Regional TB Nurse - American Lung Association of Michigan – Western and Northern Michigan (616) 942-0513
Incentives and Enablers Program	Mary Davidson, BS Program Coordinator - American Lung Association of Michigan (517) 484-7313
Detroit TB Recommendations Detroit TB Guidelines Detroit TB Policies Detroit TB Clinic	Kathy Harris, PhD, RN TB Control Program Manager – City of Detroit Health Department (313) 876-0335, ext. 122 Dee Simmons Smith CDC Public Health Advisor – City of Detroit Health Department (313) 876-0335, ext. 117
TB Medical Information	Dana Kissner, MD - **MI-ACET Chairperson** Harper University Hospital Wayne State University School of Medicine Detroit, MI (313) 745-0895 James Sunstrum, MD Oakwood TB Clinic Westland, MI (734) 727-1131
TB Laboratory Information	Dale Berry, BS TB Laboratory - MDCH Lansing, MI (517) 335-9637
TB Research	Zhenhua Yang, MD, PhD University of Michigan School of Public Health Ann Arbor, MI

Appendix J

References

1. CDC. Prevention and Treatment of TB among Patients Infected with Human Immunodeficiency Virus: Principles of Therapy and Revised Recommendations. MMWR 1998:47 (No. RR-20)
2. CDC. Updated Guidelines for the Use of Rifabutin or Rifampin for the Treatment and Prevention of TB among HIV infected Patients Taking Protease Inhibitors or Nonnucleoside Reverse Transcriptase Inhibitors. MMWR 2000; 49 (No. 9)
3. American Academy of Pediatrics. TB. In: Pickering LK, ed. 2000 Red Book: Report of the Committee on Infectious Diseases. 25th Ed.
4. DHSS. Guidelines for the Use of Antiretroviral Agents in HIV infected Adults and Adolescents. Panel on Clinical Practices for Treatment of HIV Infection 2000.
5. NJMS National TB Center. Treatment of TB: Standard Therapy for Active Disease 2000
6. American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America: Treatment of Tuberculosis. *Am J Respir Crit Care Med* 2003; 167

Appendix K

Sample Letter Request for Medical Information

(Date)

John Smith, M.D.
123 Main Street
Anywhere, MI 48888

Dear Dr. Smith:

In February, I called your office to request copies of medical records for a former patient and was told by the receptionist that I would need the family's consent. To acquaint you and your staff to Disease Reporting Rules in Michigan, I have enclosed some information. The (local health department) does have the authority to request medical records and epidemiological data via the Michigan Public Health Code. I have enclosed the salient sections of PA 368 of 1978. See section R 325.174. Also included is an abstraction of the legal code for healthcare providers titled "Guide to the Michigan Communicable Disease Rules". Specifically, page 8, section G, deals with the authority to request records and information. I hope this information will assure you that it is appropriate in the future to release this type of information to the (local health department). If you have any questions please contact me at (phone number). Thank you.

Sincerely,

Jane Doe
(Title)
Local Health Department

Michigan Advisory Committee for the Elimination of Tuberculosis (MI-ACET)

Members

Judene Bartley
MSIC
Beverly Hills, MI

Marian Beck-Clore
MDOC-Duane Waters Hosp.
Jackson, MI

Barbara Bennington
Refugee Services
Lansing, MI

Dale Berry
MDCH
Lansing, MI

Carol Bird
Oakland Co. Health Dept.
Pontiac, MI

Matthew Boulton
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Bonnie Childs
Genesee County H.D.
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